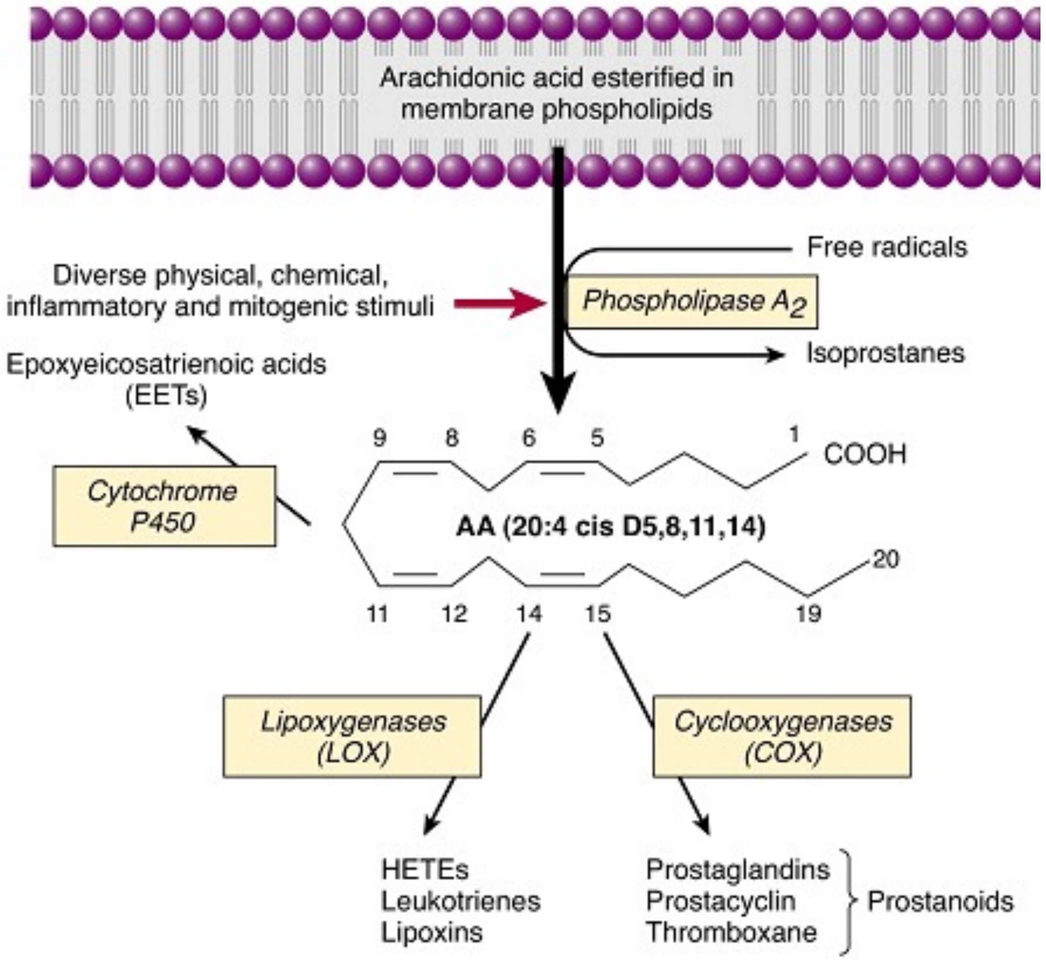
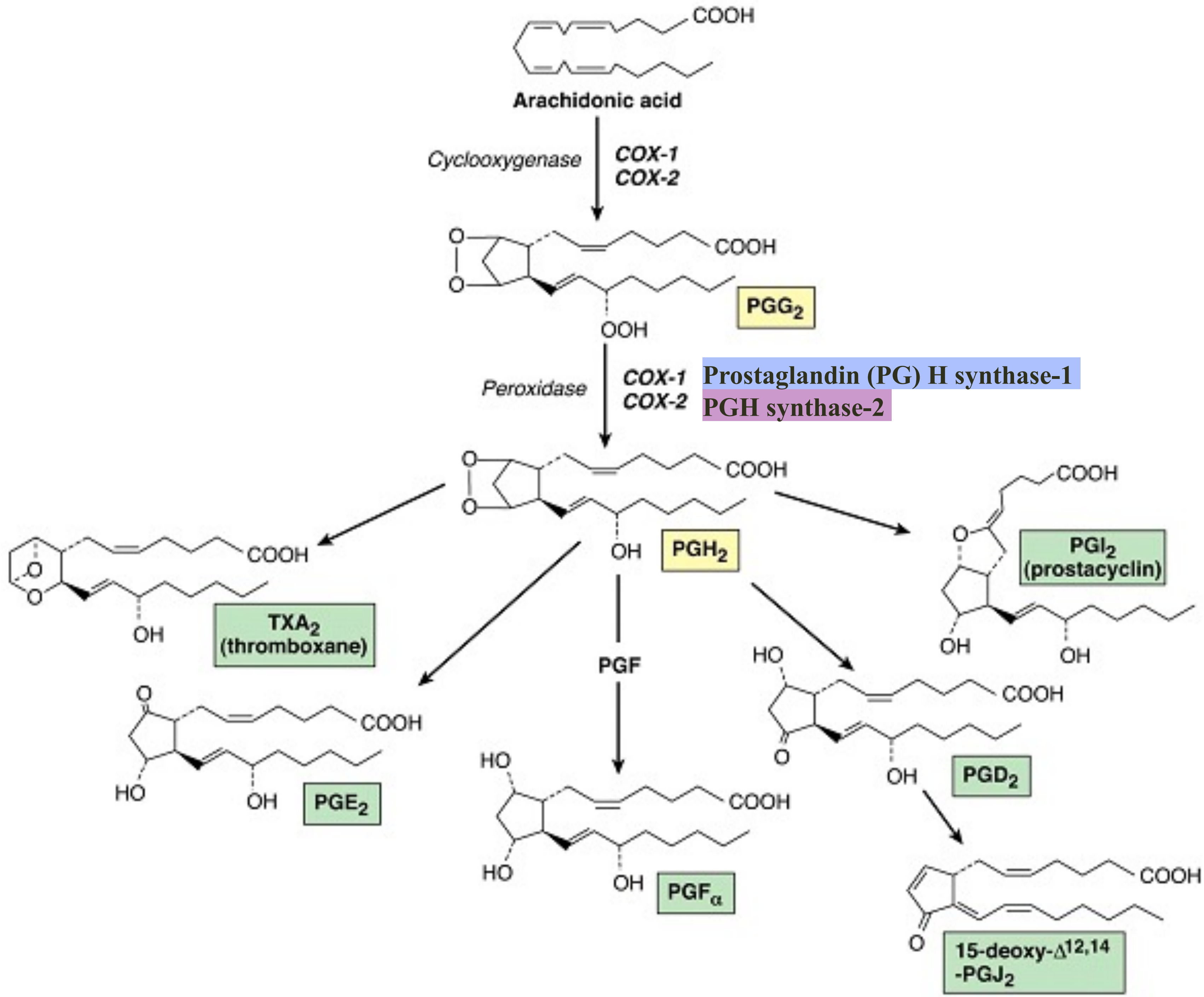
Chapter 18

The Eicosanoids: Prostaglandins, Thromboxanes, Leukotrienes, & Related Compounds

The Eicosanoids

- The eicosanoids are oxygenation products of polyunsaturated long-chain fatty acids
  - plants
  - Animals (fish)
- AA is oxygenated by four separate routes
  - cyclooxygenase (COX)
  - Lipoxygenase
  - P450 epoxygenase
  - isoeicosanoid pathways





COOH
Arachidonic acid
Cyclooxygenase
COX-1
COX-2
COOH
OOH
PGG2
Peroxidase
COX-1
COX-2
Prostaglandin (PG) H synthase-1
PGH synthase-2
COOH
OH
PGH2
COOH
O
O
OH
TXA2
(thromboxane)
COOH
PGI2
(prostacyclin)
OH
OH
PGF
O
COOH
HO
OH
PGE2
HO
COOH
HO
OH
PGFα
HO
COOH
O
OH
PGD2
COOH
O
15-deoxy-Δ12,14
-PGJ2

Cyclooxygenase

- Activity of inhibition
  - Indomethacin and sulindac
    - COX-1 > COX-2
  - Meclofenamate, ibuprofen and Aspirin
    - COX-1 = COX-2
- Inhibition of COX-2
  - celecoxib = diclofenac < rofecoxib = lumiracoxib < etoricoxib

Effects of Prostaglandins & Thromboxanes

- Smooth Muscle
  - Vascular
  - Gastrointestinal Tract
  - Airways
  - Reproductive
- Platelets
- Kidney
- Reproductive Organs
  - Female Reproductive Organs
  - Male Reproductive Organs
- Central and Peripheral Nervous Systems
  - Fever
  - Sleep
  - Neurotransmission
- Inflammation and Immunity
- Bone Metabolism
- Eye
- Cancer

Effects of Lipoxygenase & Cytochrome P450-Derived Metabolites

- Blood Cells and Inflammation
- Heart and Smooth Muscle
  - Cardiovascular
  - Gastrointestinal
  - Airways
- Renal System
- Miscellaneous

Effects of eicosanoids (Prostaglandins & Thromboxanes & Leukotrienes)

Effect	PGE_2	$PGF_{2\alpha}$	PGI_2	TXA_2	LTB_4	LTC_4	LTD_4
Major receptors	EP_{1-4}	$FP_{A,B}$	IP	TP	$BLT_{1,2}$	$CysLT_2$	$CysLT_1$
Vascular tone	↓	↑or↓	↓↓	↑↑↑	?	↑or↓	↑or↓
Bronchial tone	↓↓	↑↑	↓	↑↑↑	?	↑↑↑↑	↑↑↑↑
Uterine tone	$\uparrow_{low}$,↓	↑↑↑	↓	↑↑	?	?	?
Platelet aggregation	or		↓↓↓	↑↑↑	?	?	?
Leukocyte chemotaxis	?	?	?	?	↑↑↑↑	↑↑	↑↑

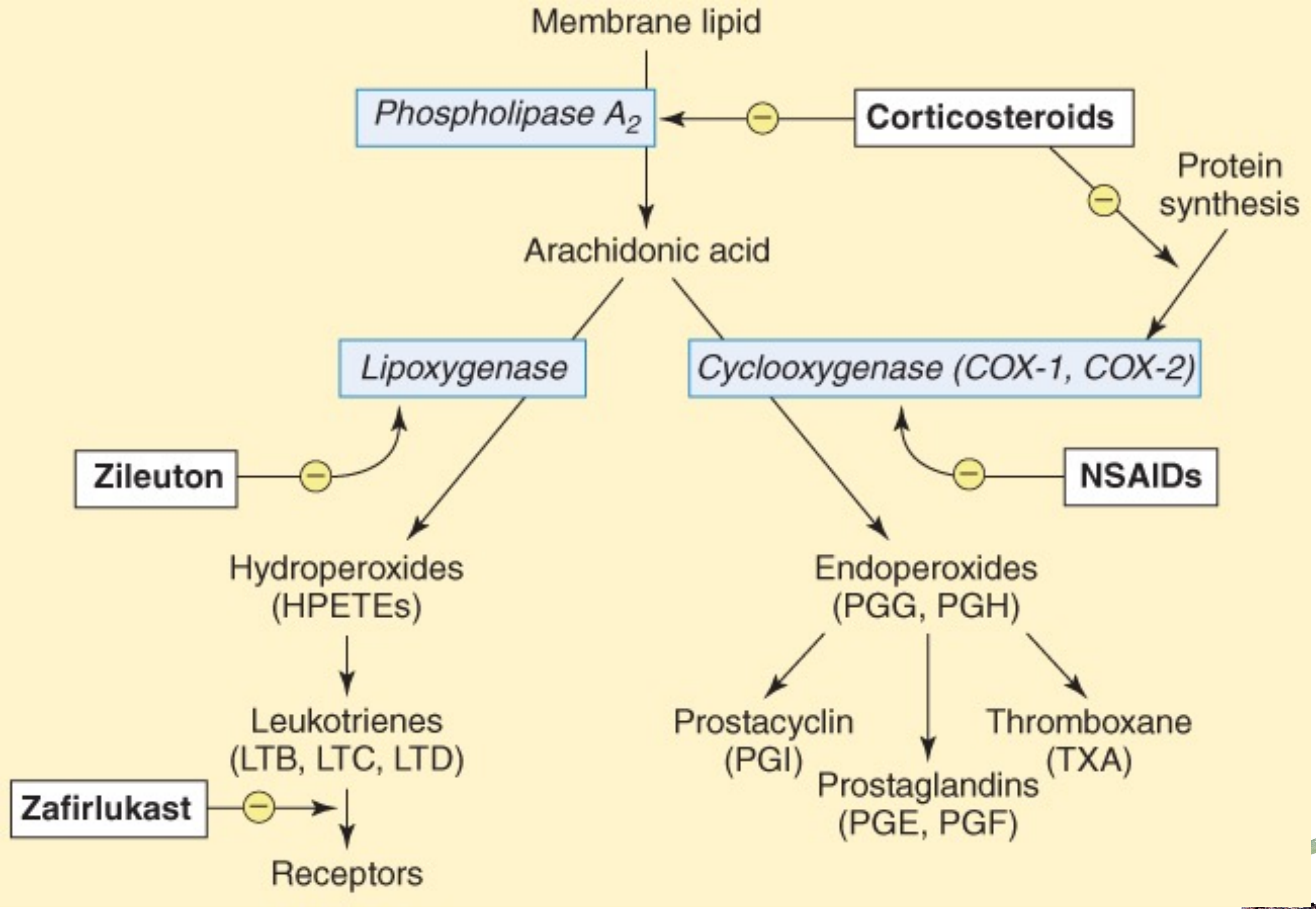
PGE_2 receptors (EPs 1–4)
$PGF_{2\alpha}$ receptor (FP)
PGI2 receptor (IP)
TXA_2 receptor (TP)
PGD_2 receptors (DP_1 and DP_2)

LTB4 receptors (BLT1 and BLT2)
cysteinyl leukotrienes (cysLT1 and cysLT2).

前列腺素之生理作用

作用	前列腺素
血管擴張 血管收縮	PGD_2 PGE_2 PGI_2 $PGF_{2\alpha}$ TXA_2
支氣管擴張 支氣管收縮	PGE_2 PGI_2 PGD_2 $PGF_{2\alpha}$ TXA_2
促進血小板凝集 抑制血小板凝集	TXA_2 PGD_2 PGI_2
子宮擴張 子宮收縮	PGE_2 PGI_2 PGE_2 $PGF_{2\alpha}$

Inhibition of Eicosanoid Synthesis



Clinical Pharmacology of Eicosanoids

- Abortion (人工流產)
  - PGE_2 and $PGF_{2\alpha}$
    - have potent oxytocic actions. The ability of the E and F prostaglandins and their analogs to terminate pregnancy at any stage by promoting uterine contractions has been adapted to common clinical use.
  - Dinoprostone
    - a synthetic preparation of PGE_2
      - Antiprogestins (eg, **mifepristone**) have been combined with an oral oxytocic synthetic analog of PGE1 (**misoprostol**) to produce early abortion
      - Side effects
        - Cramping, fetal trauma (抽筋，胎兒創傷)
  - Carboprost
      - An analog of $PGF_{2\alpha}$ is also used in obstetrics (產科學)

Mifepristone (RU486)

- 使用方法:
  - 確認懷孕(且一定要是子宮內孕)
  - 使用時機需距上次月經之第一天的49天內，需在診間醫護人員面前服藥,且須簽署同意書
  - 服完RU486, 36-48小時後服用Misoprostol (cytotec®)誘發子宮收縮，服藥後3小時內需留在醫療院所觀察
  - 病患需於2週內回診,確認完全流產

Mifepristone(RU486)

- 注意事項
  - 流產出血天數約12天，如超過兩星期,便需再做子宮清除術
  - 在兩個月內應有正常月經發生
  - 且因如此高劑量的藥物刺激,可能對胎兒造成先天的傷害，懷孕級數：X級
  - 嚴禁用在子宮外孕、氣喘、心血管疾病、 35歲以上有抽煙習慣者

- Male Reproductive System
  - **alprostadil** (PGE$_1$)
    - Mechanism of Action
      - Relaxes smooth muscle in ductus arteriosus
    - Indications
      - Transposition of great vessels, to maintain patent ductus until surgery
        - 新生兒先天性心臟缺損之緩解
      - is a second-line treatment for erectile dysfunction
    - Side effects
      - Hypotension
      - Penile pain

- Pulmonary Hypertension
  - epoprostenol (PGI_2)
    - Mechanism of Action
      - Activates IP receptors, causes vasodilation, reduces platelet aggregation
    - Indications
      - Vasodilator in pulmonary hypertension, antiplatelet agent in extracorporeal dialysis (體外透析)
    - Side effects
      - Hypotension, flushing, headache
  - Analogue
    - Iloprost
      - inhaled six to nine times per day
    - Treprostinil

- Respiratory System

A. leukotriene -receptor inhibitors (eg, zafirlukast, montelukast (Singulair®)

- Mechanism of Action
  - Block $CysLT_1$ receptor; reduce bronchoconstriction in asthma
- Indications
  - Asthma prophylaxis
- Side effects
  - GI disturbances, headache, Liver enzyme elevation…
- Note
  - Should be taken on an empty stomach. (Take at least 1 hr before or 2 hr after meals.)

MSD
SINGULAIR
montelukast sodium

MSD
SINGULAIR®
montelukast sodium

SINGULAIR
4 mg
MSD

THUR
SINGULAIR®
tablets 10 mg
欣流® 膜衣錠 10公絲
FRI
SINGULAIR®
tablets 10 mg
WED
欣流® 膜衣錠 10公絲
SAT
MSD 美商默沙東藥廠
股份有限公司台灣分公司
衛署藥輸字第022778號
TUES
SINGULAIR®
SUN
tablets 10 mg
欣流® 膜衣錠 10公絲
SINGULAIR®
MON
tablets 10 mg
欣流® 膜衣錠 10公絲
7 LOT NO.
EXP. DATE
N0903
11.2011

MSD
117
10
20

B. lipoxygenase inhibitor (zileuton)

- Mechanism of Action
  - Blocks synthesis of leukotrienes
- Indications
  - Asthma prophylaxis
- Side effects
  - Liver enzyme elevation

- Gastrointestinal System
  - Misoprostol (Cytotec®)is an orally active synthetic analog of PGE_1
    - Mechanism of Action
      - Activates EP receptors, causes increased HCO^{3-} and mucus secretion in stomach; uterine contraction
    - Indications
      - Protective agent in peptic ulcer disease
        - FDA-approved indication is for prevention of NSAID-induced peptic ulcers
      - Abortifacient (墮胎)
    - Side effects
    - Diarrhea, uterine cramping

- Glaucoma
  - Latanoprost, a stable long-acting $PGF_{2\alpha}$ derivative
    - Mechanism of Action
      - Increases outflow of aqueous humor, reduces intraocular pressure
    - Indications
      - Glaucoma
    - Side effects
      - Color change in iris

Dietary Manipulation of Arachidonic Acid Metabolism

- ω-3 fatty acid (n-3 fatty acid)
  - **Alpha-linolenic acid (ALA), EPA and DHA**
    - eicosapentaenoic (C20:5) and docosahexaenoic acids (C22:6),
- ω-6 fatty acid (n-6 fatty acid)
  - **linoleic acid (=Linolic acid)**
    - safflower, and sunflower oils, which contain linoleic acid (C18:2)
  - **Gamma-linolenic acid (GLA)**
  - **Arachidonic acid**

Omega-6 Pathway

Common in healthy diet

Linoleic acid (18:2)

↓ desaturation

γ-Linolenic acid (18:3)

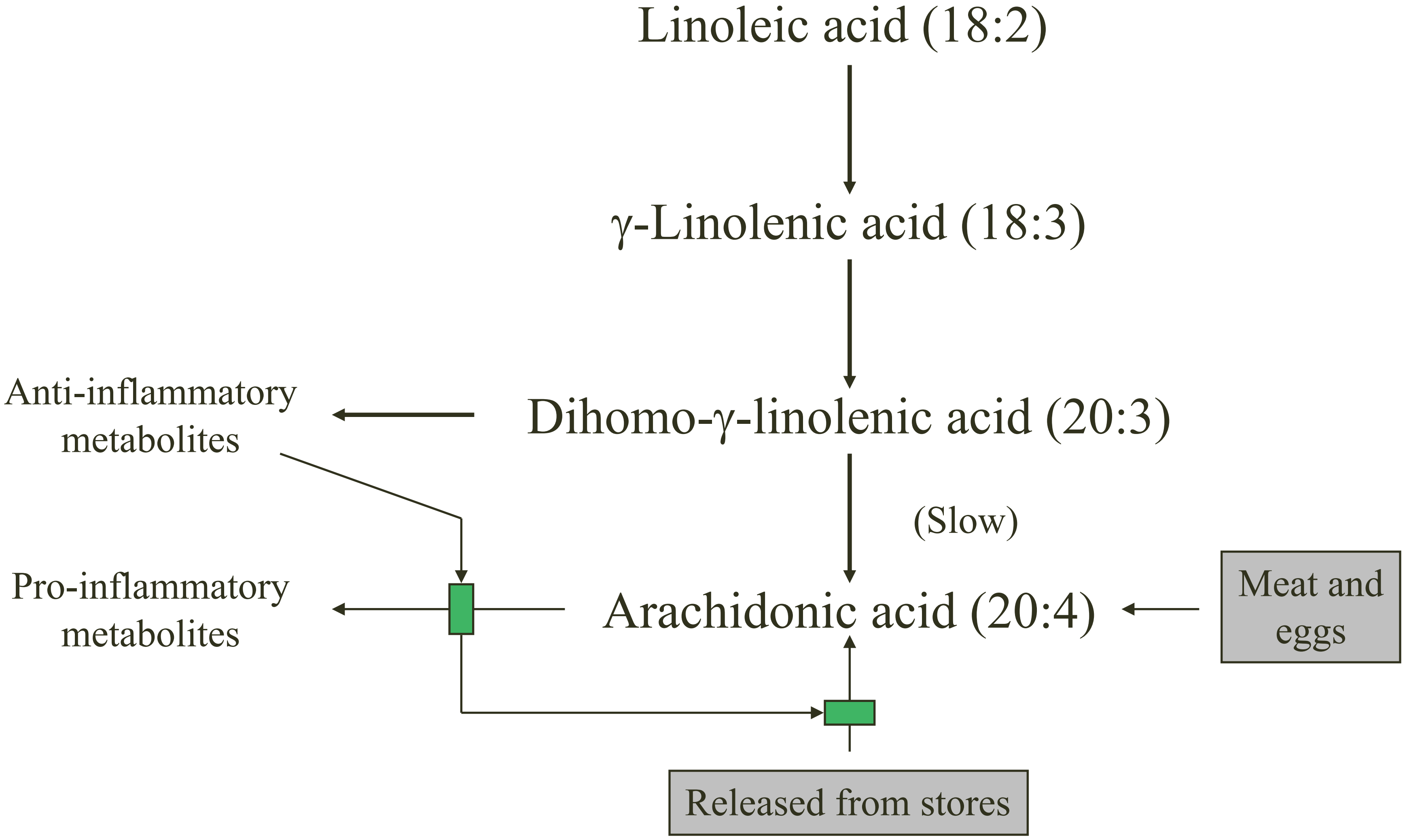
↓ elongation

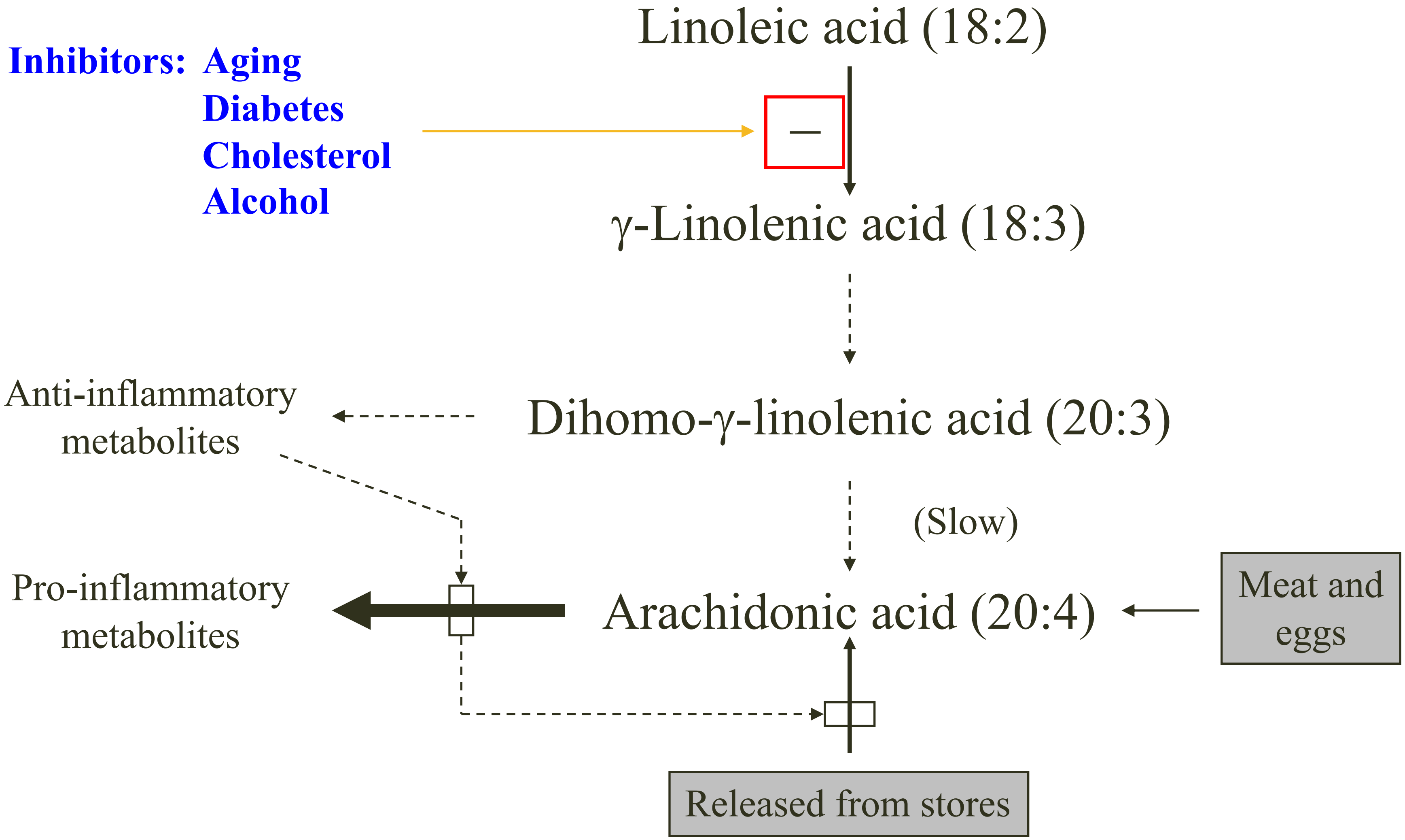
Dihomo-γ-linolenic acid (20:3)

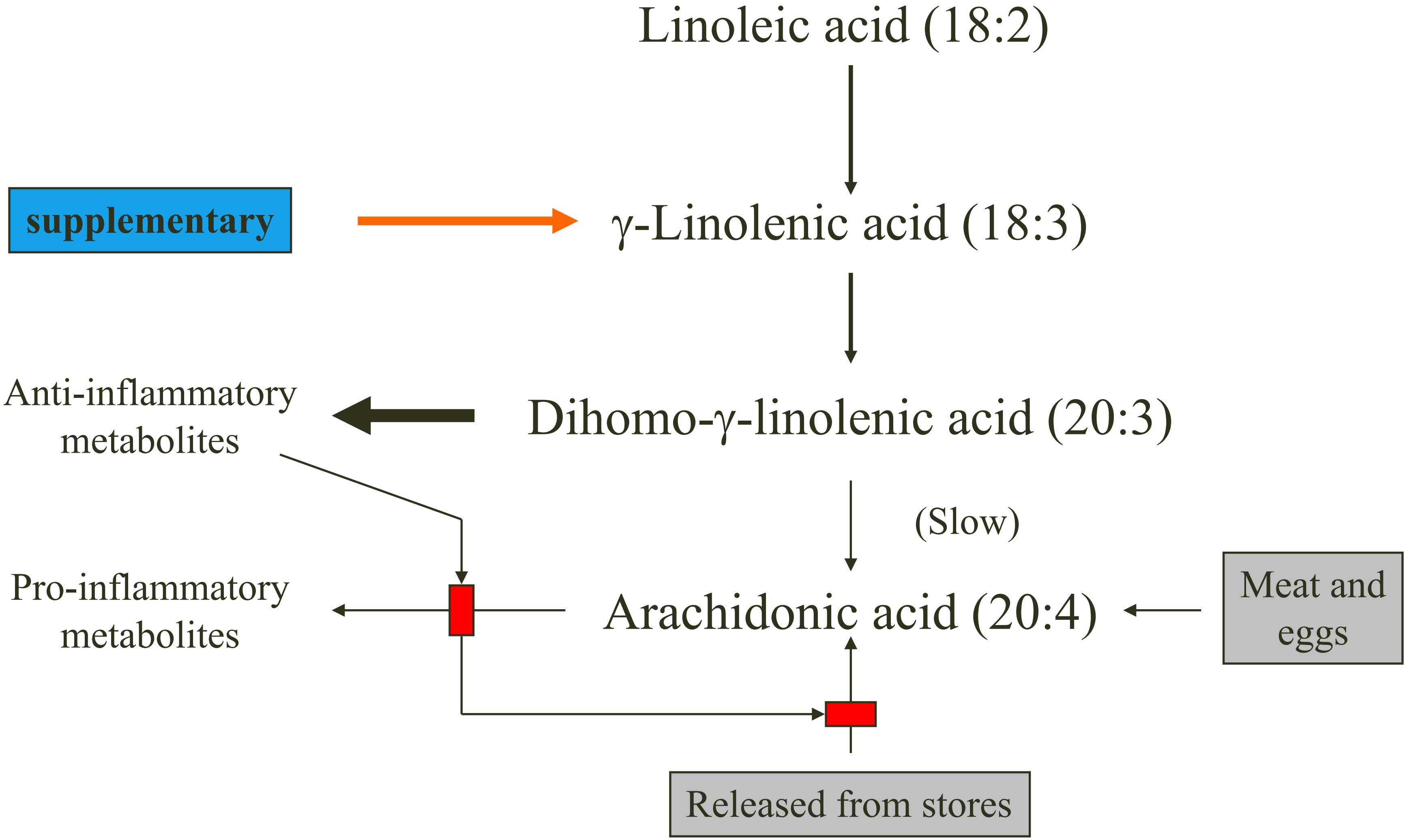
↓ desaturation

Arachidonic acid (20:4)

Some available from meat and eggs


Linoleic acid (18:2)
γ-Linolenic acid (18:3)
Anti-inflammatory metabolites
Dihomo-γ-linolenic acid (20:3)
(Slow)
Pro-inflammatory metabolites
Arachidonic acid (20:4)
Meat and eggs
Released from stores


Linoleic acid (18:2)
Inhibitors: Aging
Diabetes
Cholesterol
Alcohol
—
γ-Linolenic acid (18:3)
Anti-inflammatory
metabolites
Dihomo-γ-linolenic acid (20:3)
(Slow)
Pro-inflammatory
metabolites
Arachidonic acid (20:4)
Meat and
eggs
Released from stores


Linoleic acid (18:2)
supplementary
γ-Linolenic acid (18:3)
Anti-inflammatory metabolites
Dihomo-γ-linolenic acid (20:3)
(Slow)
Pro-inflammatory metabolites
Arachidonic acid (20:4)
Meat and eggs
Released from stores

複雜式高血壓治療

狀況	首選藥物	禁用藥物
CHF	利尿劑、ACEI 、prazosin	β-blocker (without ISA) 、reserpine
Angina	β-blocker 、Ca^{2+} antagonist	hydralazine、minoxidil、vasodilators
腦血管疾病	Ca^{2+} antagonist、hydralazine、clonidine	furosemide、α-blocker
糖尿病	ACEI 、 Ca^{2+} antagonist、prazosin	thiazide利尿劑 、non-selective β-blocker
氣喘、COPD	Ca^{2+} antagonist、vasodilators、prazosin	β-blocker
腎衰竭	ACEI 、 Ca^{2+} antagonist、prazosin	thiazide利尿劑、 β-blocker 、ACEI
性無能	ACEI 、 Ca^{2+} antagonist、 vasodilators	β-blocker
末梢血管硬化	ACEI 、 Ca^{2+} antagonist、 vasodilators	β-blocker、clonidine

Thank You !